Toyota/JAMA Comments for HEI Sponsor's Meeting

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Introduction

JAMA/JARI is interested in discussing the following subjects:

Interest of research and investigation

↑High Priority
1. Gasoline health effect (HE) study
2. In-vitro study
3. Brake/tire dust
4. Low dose effect of air pollution (threshold, acceptable level...)
5. UFP study (exposure assessment and epidemiology of UFP[PN]...)
6. Secondary aerosol formation study
7. WHO air quality guideline review
8. Effects of TRAP on nervous system (autism, dementia, Alzheimer...)
9. Health Effects of each PM source/component

➤Request for HEI comments
1. Role of ROS analysis on air pollution and its health effects studies

Gasoline HE study

● April, 2017, JAMA/JARI started a 4-year health effect study on gasoline vehicle exhaust using in vitro technique.

		2017		2018		2019		2020	
Evaluation of particle influence	Planning	▓	▓						
	Evaluation of physical properties of particles (size, mass, specific surface area)			▓	▓				
	Evaluation of chemical properties of particles (−OH, NH_2, −COOH)					▓	▓		
Evaluation of gasoline exhaust	Planning	▓	▓						
	Selection of vehicle			▓					
	Construction of equipment				▓				
	Examination of exposure condition				▓	▓			
	Evaluation of collected gasoline particles					▓	▓		
	Cell exposure of gasoline exhaust (primary only)							▓	
	Cell exposure of gasoline exhaust (including secondary PM)								▓

● What is HEI's progress on a gasoline vehicle emissions health effect (HE) study?

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Gasoline HE study: Exposure system of gasoline exhaust
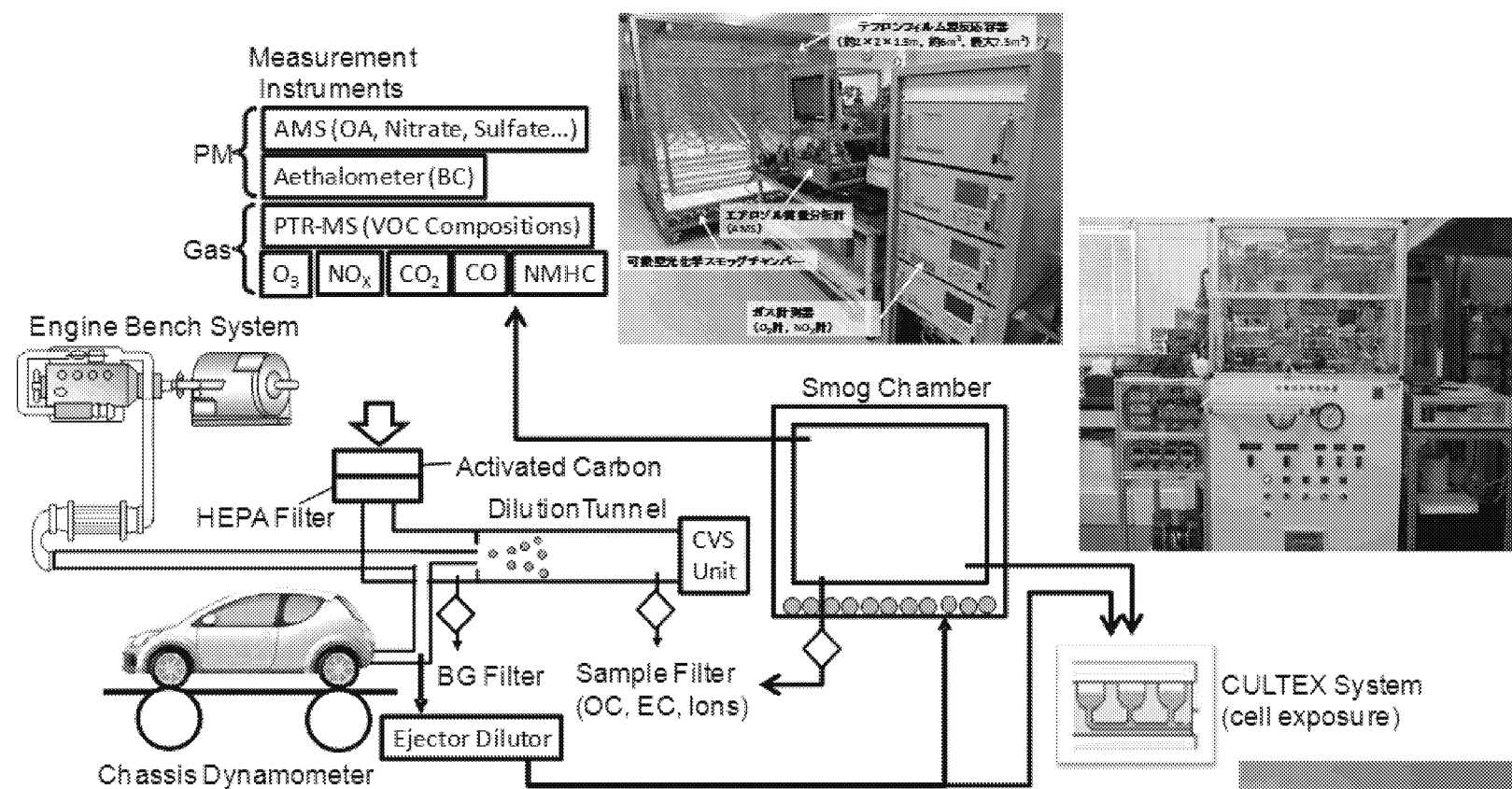
Experimental Groups
1. Clean air (Control)
2. Gasoline exhaust (nano PM exposure)
3. Gasoline exhaust reacted in the smog chamber (nano PM & 2nd PM)

In-vitro Study

- JAMA/JARI in-vitro evaluation concept study 1st phase finished March, 2017; 2nd phase began April, 2017 and will continue for 4 years.
  - Now we are studying methods to improve sensitivity and to identify the relationship between in-vitro and in-vivo.
- In Europe, there are some movement to evaluate health effects among various transportation modes using in vitro technique.
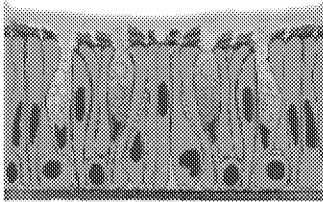
【Request for HEI comments】

- Does HEI expect to issue a request for proposals (RFA) in this area?
- What is HEI's perspective on in-vitro study?

In-vitro Study — Cell exposure and evaluation

1. Cultured cells

✓Human airway epithelial cells
- A549
- MucilAir™

MucilAir™: A Premium 3D Human Airway Epithelia reconstituted *in vitro* with Long Shelf-Life
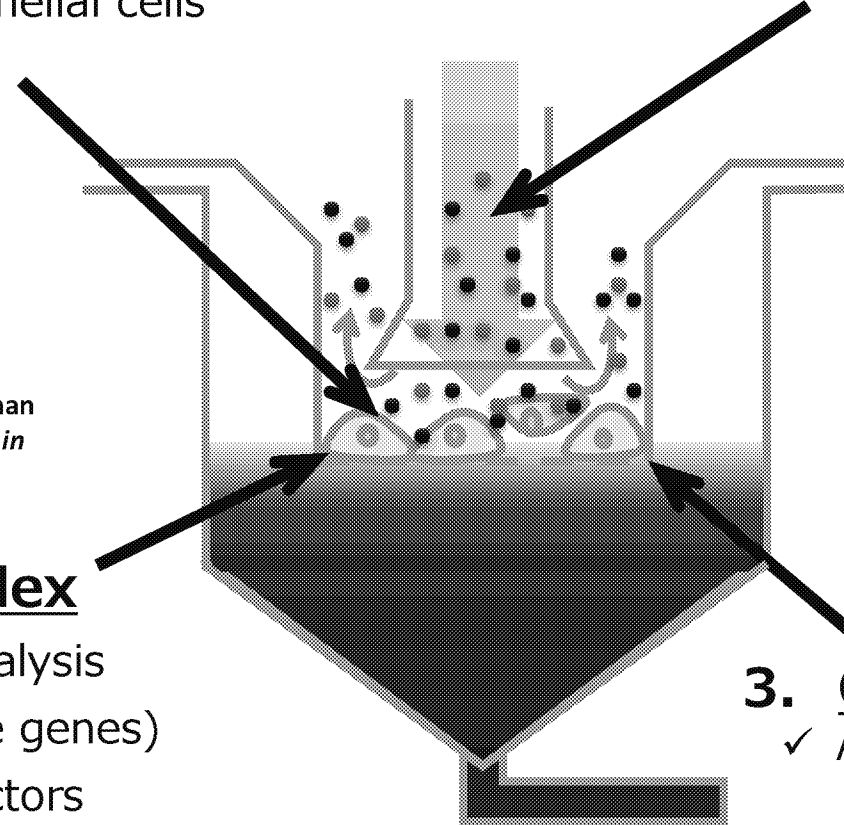
4. Evaluation index

✓Gene expression analysis
- Variability (whole genes)
- Inflammatory factors
- Cluster analysis

✓Protein analysis
- Inflammatory Cytokines

2. Exposure

✓ Worldwide harmonized Light vehicles Test Cycle (WLTC)
✓ Introduction of smog chamber
✓ Exhaust gas sampling by Ejector pump
✓ 6 hours exposure
✓ Introduction of humidifier

3. Culture method

✓ Air-liquid interface (ALI)

We focus on the *in vitro* assays to evaluate the respiratory inflammation induced by exposure to gasoline exhaust.

In-vitro Study   Time Schedule

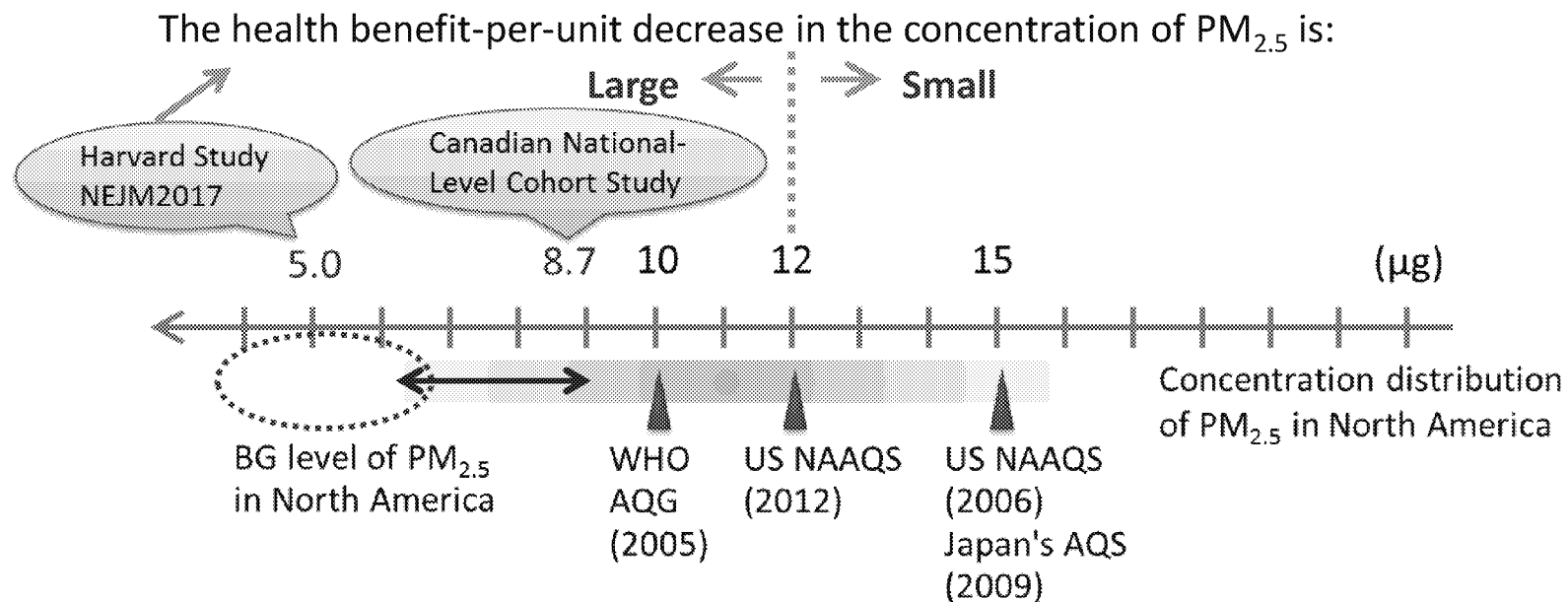|		2017	2018	2019	2020
Sensitivity improvement	**Fibroblast co-culture**	▓			
	Repetitive exposure		▓		
	Intracellular ROS analysis			▓	▓
	Evaluation of deterioration of inflammation				▓
In vitro-in vivo correlation (IVIVC)	**Research of verification method of IVIVC**	▓			
	Verification of IVIVC		▓	▓	

Brake/Tire dust

- The EU Particulate Measurement Programme (PMP) has started a discussion on how to measure brake/tire dust
- Health effect study of brake/tire dust hardly advances.
- JAMA is considering whether health effects of Brake/Tire dust is a future issue.
- JAMA is concerned about movement of brake/tire dust regulation.
- In Japan, MOE is interested in these movement of Europe.

【Request for HEI comments】

- Is there any movement in US about brake/tire dust related studies?
- Does HEI have any study plan of brake/tire dust further?

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Low dose effect of air pollution

- Epidemiological evidence on health effects of low concentration of $PM_{2.5}$ has been accumulated in the United States and Canada.

The health benefit-per-unit decrease in the concentration of $PM_{2.5}$ is:

Large ⇐ ⇒ Small

Harvard Study NEJM2017

Canadian National-Level Cohort Study

5.0   8.7   10   12   15   (µg)

BG level of $PM_{2.5}$ in North America

WHO AQG (2005)

US NAAQS (2012)

US NAAQS (2006)

Japan's AQS (2009)

Concentration distribution of $PM_{2.5}$ in North America

✓ Is a more severe $PM_{2.5}$ standard value needed for US NAAQS?

✓ Is it possible to control the level of $PM_{2.5}$ under 10 µg/m³ in the US?

【Request for HEI comments】

- How is the progress of three epidemiology studies in HEI?

- What does HEI expect the stringency of PM2.5 NAAQS to be in 2020 revision?
  If NAAQS will be strengthened, What does the PM2.5 standard value at that time?

UFP study

- EPA stance for UFP "There are still not enough data to set a UFP NAAQS." We think that this stance is not changed.

【Request for HEI comments】

- What does HEI think about EPA Stance for UFP?
- How does the influence of UFP on air quality and health effects become clear?
- Does HEI have any information about new research projects for UFP in US or Europe?
- If UFP is regulated, does the indicator become PM, PN, or other indexes?

Secondary aerosol formation study

- Dr. Robinson from CMU reported on SOA formation from gasoline vehicle at HEI work shop for Research Issues on Gasoline Exhaust Exposure last year.

  ➢ SOA production decreasing for newer vehicles.
  ➢ Lower-emitting vehicles have higher SOA yields.

【Request for HEI comments】

- What does HEI think about the vehicle contribution for Secondary Aerosol?

- What is HEI's perspective on secondary aerosol formation study?

WHO air quality guideline review

Is there an update regarding WHO air quality guideline review?

Effects of TRAP on nervous system

- ISA for PM of EPA was updated in 2018.

Table ES-1 Summary of "causal relationship" and "likely to be causal relationship" causality determinations for PM exposure and health effects from the current draft PM ISA and corresponding causality determinations from the 2009 PM ISA.

Size Fraction	Health Effect Category[a] and Exposure Duration	Causality Determination	
		2009 PM ISA	Current Draft PM ISA
$PM_{2.5}$	Respiratory Effects—Short-term exposure Section 5.1.12, Table 5-18	Likely to be a causal relationship	Likely to be a causal relationship
	Respiratory Effects— Long-term exposure Section 5.2.13, Table 5-28	Likely to be a causal relationship	Likely to be a causal relationship
	Cardiovascular Effects— Short-term exposure Section 6.1.16, Table 6-33	Causal relationship	Causal relationship
	Cardiovascular Effects— Long-term exposure Section 6.2.18, Table 6-52	Causal relationship	Causal relationship
	Nervous System Effects— Long-term exposure Section 8.2.9, Table 8-20	Not evaluated	Likely to be a causal relationship
	Cancer— Long-term exposure Section 10.2.6, Table 10-8	Suggestive of, but not sufficient to infer, a causal relationship	Likely to be a causal relationship
	Total mortality— Short-term exposure Section 11.1.12, Table 11-4	Causal relationship	Causal relationship
	Total mortality— Long-term exposure Section 11.2.7, Table 11-8	Causal relationship	Causal relationship

Changes compared to 2009

Table ES-1 (Continued): Summary of "Causal Relationship" and "Likely to be Causal Relationship" causality determinations for PM exposure and health effects from the current draft PM ISA and corresponding causality determinations from the 2009 PM ISA.

Size Fraction	Health Effect Category[a] and Exposure Duration	Causality Determination	
		2009 PM ISA	Current Draft PM ISA
UFP	Nervous System Effects— Long-term exposure Section 8.6.7, Table 8-34	Not evaluated	Likely to be a causal relationship

Change compared to 2009

ISA = Integrated Science Assessment; PM = particulate matter; $PM_{2.5}$ = fine particulate matter; UFP = ultrafine particles. Previous causality determinations taken from the 2009 PM ISA (U.S. EPA, 2009).
[a] An array of outcomes is evaluated as part of a broad health effect category: physiological measures (e.g., airway responsiveness), clinical outcomes (e.g., hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of mortality effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the evidence that supports the causality determinations and the $PM_{2.5}$ and UFP concentrations with which health effects have been associated.

【Request for HEI comments】

- How is the trend after ISA update in United States?
- Does HEI have any study plan about effects of TRAP on nervous system?

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Health Effects of each PM source/component

● There are some new study concepts on Epi-Study.

  ➢ Epidemiology by exposure evaluation that separated emission source using CMAQ

  ➢ Epidemiology by exposure evaluation that separated PM2.5 components using PMF in OEHHA

● HEI has finished N-PACT study. However the health effects on PM components have not been identified clearly yet.

【Request for HEI comments】

• What is HEI's perspective on Health Effects of each PM source/component?

• Does HEI have any plan to study this area?

Role of ROS analysis on air pollution and its health effects studies

●HEI has awarded UC-Irvine study of ROS analysis on air pollution and its health effects study.

●JAMA and JARI think the role of ROS may be important to identify the health effects of air pollution.

【Request for HEI comments】

• How can we use ROS information of air pollution as evidence of health risks (diseases) and environmental standards?

Conclusion

JAMA/JARI is interested in discussing the following subjects:

Interest of research and investigation

↑High Priority
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